The metabolic syndrome and chronic kidney disease in a Southeast Asian cohort

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US adults with metabolic syndrome, as defined by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, have been shown to be at increased risk of chronic kidney disease (CKD), but there is limited information in other populations. The relationship between metabolic syndrome and CKD (defined as estimated glomerular filtration rate <60 ml/min/1.73 m^2) was examined in a Southeast Asian cohort. This relationship was examined when the subjects ($n=3195$) were initially recruited in a cross-sectional analysis. The risks of developing new CKD associated with metabolic syndrome were also examined prospectively in a subgroup ($n=2067$) without CKD at entry after 12 years follow-up. Metabolic syndrome was defined according to both NCEP ATP III and the new International Diabetes Federation (IDF) criteria. The prevalence of CKD was 1.6%, and the incidence of new CKD was 6.3%. Metabolic syndrome by NCEP ATP III definition was associated with the increased risk of CKD at baseline (adjusted odds ratio (OR) 2.48 and 95% confidence interval 1.33–4.62), and of developing new CKD at follow-up (adjusted OR 1.62 and 95% confidence interval 1.00–2.61). There was a significant graded relationship between the number of metabolic syndrome components present and risk of CKD. By contrast, metabolic syndrome by IDF definition was not associated with increased risk of CKD. These results suggest the relationship between CKD and metabolic syndrome in a Southeast Asian population is highly dependent on the criteria used to define metabolic syndrome.

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Individuals with metabolic syndrome are at increased risks for developing cardiovascular diseases, stroke, and cardiovascular mortality.[1] Although the concept of metabolic syndrome is widely used, several definitions of the syndrome exist. These definitions agree on the essential components of metabolic syndrome, but differ in the criteria used in the classification. In 2001, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) recommended the use of five variables such that individuals with any three or more out of five components are classified as having metabolic syndrome. A modified NCEP definition with a lower cutoff threshold for waist circumference has been recommended in Asian populations.[2]

More recently, the International Diabetes Federation (IDF) has proposed a new definition of metabolic syndrome.[3] The IDF definition retained four of the five NCEP ATP III criteria, but decreased the threshold for high fasting glucose.[4] In addition, the IDF definition requires the presence of obesity using an ethnic-origin-specific threshold for waist circumference plus any two or more of the other four components. Although the IDF definition aims to produce a single, universally accepted diagnostic tool to address both clinical and research needs, more information is required about its role in predicting clinical events in prospective settings.

Changes in lifestyle and diet have led to an increase in prevalence of metabolic syndrome in many parts of the world including Asia.[5] In China alone, 64 million people are currently estimated to have metabolic syndrome.[6] Globally, a rise in the incidence of chronic kidney disease (CKD) and end-stage renal disease in recent years paralleled increasing prevalence of metabolic syndrome.[1,7] Both cross-sectional[8] and prospective[9] studies of US adults have demonstrated that individuals with metabolic syndrome are at increased risk of CKD. However, there are sparse data on the risks of CKD associated with the metabolic syndrome in the non-US populations. The present report will examine the relationship between CKD and metabolic syndrome as differently defined by either NCEP or IDF in a specific Southeast Asian cohort. We will examine this relationship both cross-sectionally, with regards to the prevalence of CKD when the subjects were

initially recruited and prospectively, with regards to the incidence of new CKD after 12 years of follow-up.

RESULTS

Baseline characteristics

All subjects. Seventy-five subjects were on antihypertensive therapy. No subjects were taking HMG-Co A reductase inhibitors. Figure 1a shows the frequencies of metabolic syndrome and the number of metabolic syndrome components present among the 3195 subjects with complete baseline data in 1985. Overall, 13.2% had metabolic syndrome by NCEP ATP III criteria (METS-NCEP$_{ATP\ III}$), 19.4% had METS-NCEP$_{Mod}$, and 12.2% had METS-IDF, respectively.

New CKD subgroup. In the 1997 survey, 145 subjects had died and 301 subjects were lost to follow-up. A total of 682 subjects were excluded because they either had CKD at entry or incomplete follow-up data. Figure 1b shows the frequencies of metabolic syndrome and the numbers of metabolic syndrome components present at entry in the 2067 subjects with complete data included in the *New CKD subgroup*. In this subgroup, 11.0% had METS-NCEP$_{ATP\ III}$, 16.9% had METS-NCEP$_{Mod}$, and 10.6% had METS-IDF at baseline.

Table 1 presents the baseline characteristics of all subjects and the *New CKD subgroup* by metabolic syndrome status at entry. Subjects with METS-NCEP$_{ATP\ III}$ were older, and had higher proportion of men compared with subjects without, in all subjects and in the *New CKD subgroup*.

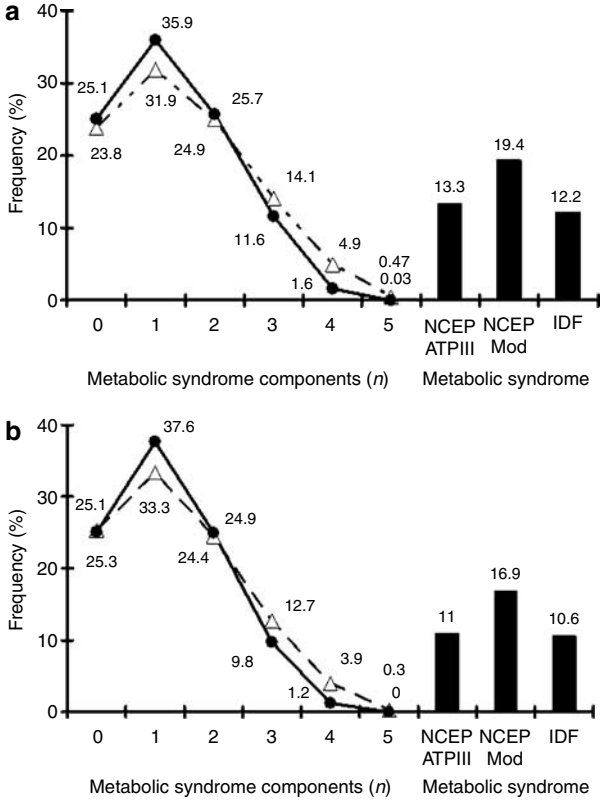

Figure 1 | Distribution of metabolic syndrome components. The proportion with metabolic syndrome and the number of metabolic syndrome components at entry among (**a**) all subjects ($n = 3195$) and (**b**) New CKD subgroup ($n = 2067$). The number of components shown according to ATP III criteria (solid line, solid circles) or modified criteria (dash line, open triangle). Filled columns denote frequency of metabolic syndrome by different definitions. NCEP$_{ATP\ III}$, metabolic syndrome by NCEP ATP III criteria; NCEP$_{Mod}$, NCEP modified criteria; IDF, IDF criteria.

Relationship between metabolic syndrome and the prevalence of CKD at baseline

Among all subjects, there was 1.6% who had CKD at baseline. Figure 2a shows the prevalence of CKD by different definitions of the metabolic syndrome. The prevalence of CKD was increased in subjects with METS-NCEP$_{ATP\ III}$ or METS-NCEP$_{Mod}$ compared with subjects without ($P < 0.01$ for each). By contrast, subjects with METS-IDF did not have increased prevalence of CKD.

Table 2 shows odds ratios (ORs) for the prevalence of CKD in all subjects at baseline associated with individual component, and with different definitions of metabolic syndrome. In the unadjusted model, high blood pressure (BP), high triglycerides (TG), and high fasting glucose (FG)-NCEP were associated with increased odds of CKD at baseline. After adjustment for age, sex, and smoking status, the prevalence of CKD at entry depended on high BP, METS-NCEP$_{ATP\ III}$, and METS-NCEP Mod. METS-IDF was not associated with increased risk for CKD. Figure 3a showed that the adjusted ORs of prevalence of CKD increased with the numbers of components of metabolic syndrome present (P for trend < 0.05 for both NCEP ATP III and NCEP Modified definitions).

Relationship between metabolic syndrome and the incidence of new CKD at follow-up

New CKD developed in 6.3% after 12 years. Figure 2b shows the incidence of new CKD at follow-up by different definitions of metabolic syndrome at entry. The incidence of new CKD was higher in subjects with METS-NCEP$_{ATP\ III}$ or METS-NCEP$_{Mod}$ compared with subjects without ($P < 0.05$ for each). By contrast, subjects with METS-IDF did not have significantly increased incidence of new CKD.

Table 3 shows ORs for the development of new CKD associated with individual component, and with different definitions of metabolic syndrome. In the unadjusted model, high TG and high FG -NCEP were associated with increased risk for new CKD. After adjustment for age, sex, and smoking status, the development of new CKD at follow-up was associated with high FG-NCEP and METS-NCEP$_{ATP\ III}$. Subjects with METS-NCEP$_{Mod}$ had 1.3-fold increased risk of new CKD, but this was not significant ($P = 0.16$). Subjects with METS-IDF had no increased risk for developing new CKD. Figure 3b showed that the adjusted ORs of new CKD incidence increased with the numbers of components of metabolic syndrome present at baseline (P for trend < 0.05 for both NCEP ATP III and NCEP Modified definitions).

Table 1 | Baseline characteristics of study subjects with or without METS-NCEP$_{ATP\ III}$

	All subjects			New CKD subgroup		
Characteristics (*N*)	METS-NCEP$_{ATP\ III}$ present (424)	METS-NCEP$_{ATP\ III}$ absent (2771)	*P*-value	METS-NCEP$_{ATP\ III}$ present (227)	METS-NCEP$_{ATP\ III}$ absent (1840)	*P*-value
Age (years)	43.8±5.1	42.3±4.8	<0.001	43.0±4.8	41.7±4.5	<0.001
Male subjects (%)	88	78	<0.001	87	75	<0.001
Tobacco use, current (%)	47	45	NS	43	40	NS
Diabetic (%)	12	1	<0.001	9.3	1.1	<0.001
Systolic BP (mm Hg)	132.0±14.4	118±15.5	<0.001	130.6±13.1	118.4±15.2	<0.001
Diastolic BP (mm Hg)	83.9±9.0	73.8±10.7	<0.001	83.6±8.4	73.7±10.7	<0.001
Body mass index (kg/m^2)	25.8±3.5	22.6±2.8	<0.001	25.6±3.3	22.5±2.7	<0.001
Waist circumference (cm)	88.4±8.7	79.3±8.6	<0.001	87.7±8.2	78.8±8.6	<0.001
Fasting glucose (mg/dl)	99.9±33.6	88.1±13.5	<0.001	97.6±30.7	87.8±13.2	<0.001
Total cholesterol (mg/dl)	234.8±43.7	220.4±41.7	<0.001	232.6±43.1	220.0±41.4	<0.001
LDL-c (mg/dl)	151.4±41.5	145.8±40.1	0.01	150.9±41.2	146.3±39.5	NS
HDL-c (mg/dl)	35.8±6.9	48.6±11.3	<0.001	35.3±6.2	48.6±11.2	<0.001
Triglycerides (mg/dl)	265.7±82.6	134.7±81.9	<0.001	247.7±117.7	129.6±74.8	<0.001
Creatinine (mg/dl)	0.95±0.20	0.88±0.20	<0.001	0.92±0.19	0.87±0.18	<0.001
eGFR (ml/min per 1.73 m^2)	93.9±4.2	99.9±24.0	<0.001	97.0±24.6	100.7±23.9	0.04

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; METS-NCEPATP III, metabolic syndrome by NCEP ATP III definition; NS, nonsignificant.
Continuous data are shown as mean±s.d.

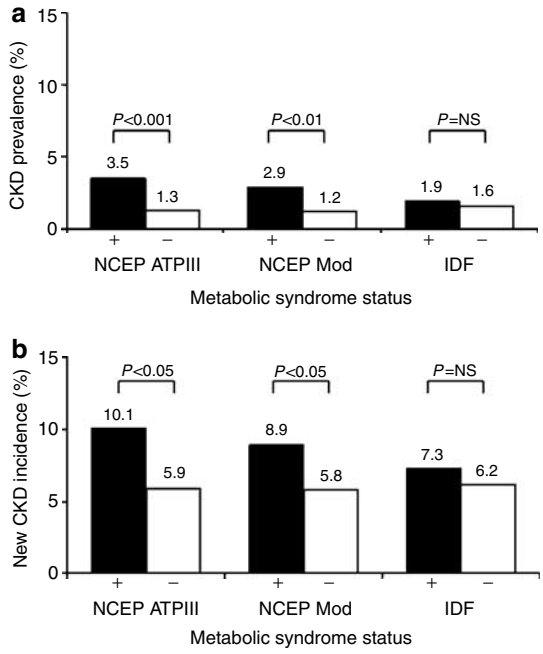

Figure 2 | Chronic kidney disease frequency and metabolic syndrome. (**a**) The prevalence of CKD at entry in all subjects ($n=3195$) and (**b**) the incidence of new CKD after 12 years in the new CKD subgroup ($n=2067$) according to the presence (+, dark columns) or absence (−, light columns) of metabolic syndrome. CKD, chronic kidney disease; NCEP$_{ATP\ III}$, metabolic syndrome by NCEP ATP III criteria; NCEP$_{Mod}$, metabolic syndrome by NCEP modified criteria; IDF, metabolic syndrome by IDF criteria.

The risks of CKD associated with specific combinations of metabolic syndrome components

To further investigate which components are actually predictive, we compared the ORs of CKD owing to all possible combinations of three NCEP metabolic syndrome components with subjects having zero components. The ORs of CKD for statistically significant combinations of components are shown in Table 4. In the prevalence study, 802 and 762 subjects had zero metabolic syndrome components by NCEP ATP III and NCEP modified criteria, respectively. Compared with subjects with zero factors, subjects with selected combinations had the 8-to 12-fold higher risk of prevalence of CKD. Although the numbers with each of these combinations accounted for only 1–2% of the study subjects, the OR of CKD prevalence in subjects with these combinations was 1.5- to fourfolds higher than when these components are considered individually or nearly twofold higher than subjects with metabolic syndrome by NCEP ATP III definition.

For the new CKD study, 547 and 524 subjects had zero metabolic syndrome components by NCEP ATP III and NCEP modified criteria, respectively. Subjects with high FG-NCEP + high BP + high TG or subjects with high FG-NCEP + high TG + obesity Asia had the highest risks of new CKD. Subjects with these combinations had six- to sevenfold higher odds of new CKD compared with subjects with zero factors. Only 0.5–1.3% of the study group had these combinations, but the risk of new CKD in these subjects were about 2.5-fold higher than subjects with metabolic syndrome by NCEP ATP III definition.

DISCUSSIONS

This study identified a positive relationship between metabolic syndrome by NCEP ATP III definition and risk of CKD at baseline, and such was carried also after 12 years of follow-up in a Thai cohort. This risk is independent of confounding factors, such as age, sex, and smoking status. By contrast, when the IDF criteria are used, no relationship is observed between metabolic syndrome and CKD.

Table 2 | Odds ratios for the prevalence of chronic kidney disease from all study subjects (*n*=3195)

Variable	*N* with variable	Unadjusted	95% CI	*P*-Value	Adjusted[a]	95% CI	*P*-value
High BP	1622	2.29	1.25–4.21	0.008	1.95	1.05–3.62	0.03
Low HDL-c	1075	1.56	0.89–2.74	NS	1.62	0.92–2.85	NS
High TG	1180	1.87	1.07–3.27	0.03	1.61	0.91–2.84	NS
High FG-IDF	426	1.44	0.69–2.98	NS	1.21	0.58–2.53	NS
High FG-NCEP	165	2.56	1.08–6.10	0.03	2.03	0.84–4.88	NS
Abdominal obesity-ATP III	73	0.87	0.41–6.4	NS	0.78	0.11–5.73	NS
Abdominal obesity-Asia	611	1.06	0.53–2.13	NS	0.87	0.43–4.77	NS
METS-NCEP$_{ATP\ III}$	424	2.87	1.55–5.3	0.001	2.48	1.33–4.62	0.004
METS-NCEP$_{Mod}$	624	2.38	1.33–4.26	0.004	2.00	1.10–3.63	0.02
METS-IDF	390	1.59	0.77–3.30	NS	1.28	0.61–2.69	NS

BP, blood pressure; CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; METS-IDF, metabolic syndrome by IDF criteria; METS-NCEP$_{ATP\ III}$, metabolic syndrome by NCEP ATP III criteria; MET-NCEP$_{Mod}$, metabolic syndrome by NCEP modified criteria; NS, nonsignificant; TG, triglycerides.
Criteria for individual component of metabolic syndrome defined in the text.
[a]Adjusted for age, sex, smoking status.

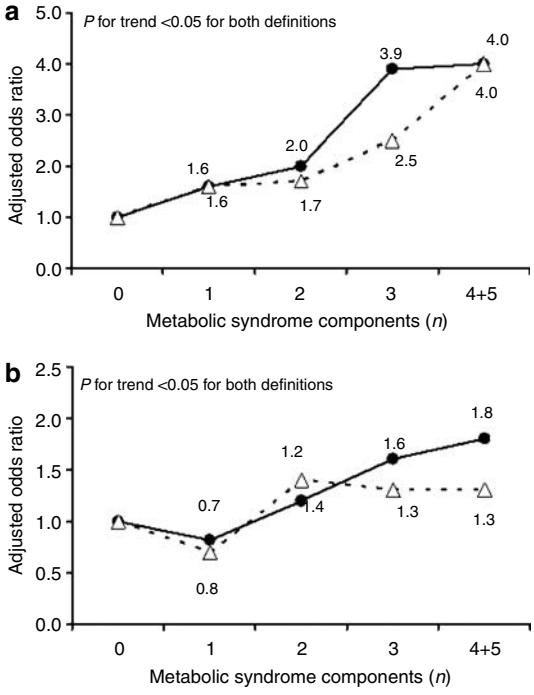

Figure 3 | Risks of chronic kidney disease. The ORs adjusted for age, sex, and smoking status of (**a**) CKD at baseline and (**b**) New CKD after 12 years by the number of metabolic syndrome components present at entry. Numbers of components are defined by either NCEP ATP III (solid line, solid circles) or NCEP Modified criteria (Dash line, open triangle).

To the best of our knowledge, this is the first analysis of the relationship between CKD and metabolic syndrome in a Southeast Asian cohort using a clinically meaningful end point (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2) rather than surrogate markers of renal injury, and the first study to examine the IDF criteria of metabolic syndrome with regards to risks of CKD. Previously, the risks of CKD associated with metabolic syndrome as defined by NCEP ATP III had been examined in cross-sectional studies from the US[8] and Japan,[10] and in a single prospective study from the US.[9] The prevalence of CKD and incidence of new CKD in our subjects are comparable to the US studies.[8,9] The prevalence of obesity and metabolic syndrome by both NCEP ATP III, NCEP modified and IDF criteria observed in our cohort are similar to Chinese[6] and other Asian populations.[11] This contrasts with a higher prevalence of 25–40% for metabolic syndrome by both NCEP ATP III or IDF definitions in the US population.[8,9,12]

Similar to the US studies, we found that the risk for CKD increased with higher numbers of metabolic syndrome components.[8,9] In our subjects with metabolic syndrome by NCEP ATP III definition, the magnitude of risk for CKD in both cross-sectional and prospective analyses is comparable to the US studies. The higher ORs of CKD observed in the cross-sectional analyses compared with prospective analyses likely reflect the fact that metabolic syndrome may not only predispose to CKD, but also that CKD increases the frequency of hypertension, dyslipidemia, and impaired glucose tolerance, and hence the prevalence of metabolic syndrome.[7] When we used the modified NCEP criteria[13] instead of ATP III, the numbers of persons classified as having metabolic syndrome increased, but the magnitude of risk for CKD tended to decrease. These findings are similar to a study from Japan, in which subjects with metabolic syndrome by NCEP ATP III definition had increased risk of CKD, whereas subjects with metabolic syndrome by the modified NCEP definition did not.[10] Thus, unlike for cardiovascular diseases, more data are needed before the modified NCEP criteria can be applied to predict kidney diseases in Asian subjects.

The NCEP definition gives equal weight to each metabolic syndrome component. However, the prevalence and the impact of each component may vary substantially between different ethnic groups. In the US population, each individual component of the metabolic syndrome is associated with increased risk of CKD, albeit with different magnitude.[8,9] Experimental and epidemiologic studies that show that hypertension and diabetes lead to CKD are well described.[14,15] In our study, when risk factors were considered individually after adjustments for age and sex, elevated BP was associated with increased adjusted risk of prevalence of CKD, and elevated fasting glucose was

Table 3 | Odds ratios of developing new chronic kidney disease (12 years follow-up) for the New CKD subgroup (*n*=2067)

Variable	*N* with variable	Unadjusted	95% CI	*P*-value	Adjusted[a]	95% CI	*P*-value
High BP	1012	1.38	0.94–1.91	NS	1.16	0.81–1.67	NS
Low HDL-c	683	1.19	0.82–1.71	NS	1.25	0.87–1.82	NS
High TG	695	1.47	1.02–2.10	0.04	1.26	0.88–1.82	NS
High FG-IDF	252	1.59	0.99–2.54	0.05	1.38	0.85–2.22	NS
High FG-NCEP	89	2.44	1.29–4.60	0.006	1.97	1.03–3.78	0.04
Abdominal obesity-ATP III	35	0.90	0.21–3.78	NS	0.82	0.19–3.46	NS
Abdominal obesity-Asia	361	1.44	0.94–2.20	NS	1.24	0.08–1.91	NS
METS-NCEP$_{ATP\ III}$	227	1.81	1.13–2.90	0.01	1.62	1.00–2.61	0.049
MET-NCEP$_{Mod}$	249	1.58	1.04–2.40	0.03	1.36	0.88–2.08	NS
METS-IDF	220	1.18	0.69–2.04	NS	0.97	0.56–1.69	NS

BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; METS-IDF, metabolic syndrome by IDF criteria; METS-NCEP$_{ATP\ III}$, metabolic syndrome by NCEP ATP III criteria; MET-NCEP$_{Mod}$, metabolic syndrome by NCEP modified criteria; NS, nonsignificant; TG, triglycerides.
Criteria for individual components of metabolic syndrome defined in the text.
[a]Adjusted for age, sex, smoking status.

Table 4 | OR of CKD prevalence in all study subjects (*n*=3195) and of developing new CKD in subgroup (*n*=2067) associated with different combinations of metabolic syndrome components

Prevalence components	*N* with parameter	OR	*P*-value	New CKD components	*N* with parameter	OR	*P*-value
High FG-NCEP +high BP +high TG	61	11.9	<0.001	High FG-NCEP +high TG +abdominal Obesity-Asia	10	7.32	0.02
High FG-NCEP +high BP +low HDL-c	41	10.5	0.007	High FG-NCEP +high BP +high TG	26	6.35	<0.001
High FG-NCEP +high BP +abdominal obesity-Asia	44	9.22	0.01				
High FG-NCEP +high TG +abdominal obesity-Asia	31	8.69	0.04				
High BP +low HDL-c +high TG	341	4.01	0.006				
High FG-NCEP	165	5.01	NS	High FG-NCEP	89	2.69	0.01
High BP	1622	2.92	0.01	High BP	1012	1.24	NS
Low HDL-c	1075	2.77	0.02	Low HDL-C	683	1.30	NS
High TG	1180	2.99	0.01	High TG	695	1.48	NS
Abdominal obesity-ATP III	73	1.84	NS	Abdominal obesity-ATP III	35	1.04	NS
Abdominal obesity-Asia	611	2.10	NS	Abdominal obesity-Asia	361	1.56	NS
METS-NCEP$_{ATP\ III}$	424	4.87	<0.001	METS-NCEP-$_{ATP\ III}$	227	1.94	0.02
METS-NCEP$_{Mod}$	620	3.77	0.003	METS-NCEP$_{Mod}$	349	1.66	NS
IDF	390	2.97	0.03	IDF	220	1.34	NS

BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; HDL-c, high-density lipoprotein cholesterol; IDF, International Diabetes Federation; METS-IDF, metabolic syndrome by IDF criteria; METS-NCEP$_{ATP\ III}$, metabolic syndrome by NCEP ATP III criteria; MET-NCEP$_{Mod}$, metabolic syndrome by NCEP modified criteria; NS, nonsignificant; OR, odds ratio.
Criteria for individual components of metabolic syndrome by NCEP criteria as defined in the text. Odds ratios are derived from comparisons with subjects with zero components as defined according to NCEP ATP III criteria except when abdominal obesity-Asia is used, when NCEP Modified criteria is used instead. Only significant combinations of factors are shown.

associated with increased risk of new CKD. Combinations of elevated fasting glucose with other metabolic syndrome risk factors appeared to have additive effects on the risks of CKD. This is consistent with previous studies, which have shown that the risk of diabetes mellitus-induced renal damage is high in Asian subjects.[16] Indeed, in Thailand, as in many parts of Asia, diabetes has emerged as the leading cause of end-stage renal disease.[17] Several lines of evidence suggest that dyslipidemia may be an important factor for the development and progression of CKD.[18,19] Although not statistically significant, we also show a trend for association with CKD for low high-density lipoprotein cholesterol (HDL-c) and high TG with similar magnitude of adjusted risk as the US studies.[8,9]

Central obesity and insulin resistance are hypothesized as important causative factors for metabolic syndrome.[1] The importance of obesity in the development and progression of CKD has been suggested by animal studies,[7] and by the development of focal segmental glomeruloscerosis in some obese human subjects.[20] Obesity has been shown to be a risk factor for end-stage renal disease, but this has not been a consistent finding.[21,22] In the US population, obesity was associated with increased prevalence of CKD.[8] However, even in the US population, the direct role of obesity as a risk factor for new CKD might be marginal, as the confidence interval of the adjusted OR for obesity as a risk of developing new CKD included 1.00.[9] In our study, obesity was not associated with CKD. The number of subjects with ATP III definition of obesity was very low compared with the US studies.[8,9] Thus, the apparent lack of effect of obesity in our study could be ascribed to the lower number of obese subjects and the lower degree of obesity rather than the lack of effects of obesity on

CKD development *per se*. Although not significant by itself, the presence of obesity might increase the risk of CKD in the presence of other metabolic syndrome risk factors.

By requiring the presence of obesity as an essential component, the IDF definition attempts to increase the specificity for the diagnosis of metabolic syndrome as a predictor of cardiovascular diseases and reduce the possibility of over-diagnosing subjects who happen to have a clustering of other components in the absence of obesity.[3] In the US subjects, the prevalence of coronary heart disease is increased in subjects with metabolic syndrome whether defined by IDF or by NCEP ATP III.[12] The relationship of metabolic syndrome by IDF definition and CKD has not been tested. Compared with subjects without metabolic syndrome, our subjects with metabolic syndrome by IDF definition did not have increased adjusted risk of CKD, although these subjects had increased risks of cardiovascular events (W Aekplakorn, unpublished observations). The differences in risks of CKD observed between NCEP and IDF definitions raises important questions about the meaning of the concept of metabolic syndrome, specifically, whether obesity should be a prerequisite for the diagnosis. In addition, the risks of CKD were higher with specific combinations of metabolic syndrome components compared with current metabolic syndrome definitions. Thus, the 1–2% of subjects with combinations of elevated glucose and high TG, and high BP or subjects with elevated glucose and high TG, and obesity by Asian criteria consistently had the highest risks for both prevalence and incidence of new CKD. Thus, whether the metabolic syndrome concept provides advantages over the analysis of specific combinations of risk factors with regard to CKD deserves further studies.

Limitations to our study should be noted. First, in the second survey, not all individuals who participated in the first survey returned for follow-up. As individuals who did not have complete data were likely to be older or have metabolic syndrome (data not shown), exclusion of these individuals would be expected to bias the prospective data to the null. Second, the analyses were based mainly on the data obtained from the first survey. The variability of the studied risk factors was uncertain over the 12 years interval. Third, we used eGFR rather than directly measured GFR to define CKD. This process requires that the serum creatinine (sCr) be calibrated by an indirect method to a US population data. The relationship between sCr and GFR varies with race, and the modification of diet in renal disease formula has not been validated in a Thai population. Fourth, our population consists mostly of middle-aged men with low prevalence of obesity and CKD. It is possible that relative contribution of metabolic syndrome or obesity could be different in a population with higher proportion of women or older subjects. Despite these limitations, both our cross-sectional and prospective data are consistent with other published series. Nonetheless, we cannot exclude the possibility that with larger numbers of subjects, an effect for obesity or metabolic syndrome according to the IDF definition would be seen.

In conclusion, the risks of CKD associated with metabolic syndrome depend on the definition of metabolic syndrome used. The contribution of obesity on the risk of CKD in our population appears to be less than the US population. It is uncertain if this relationship will change if the proportion of subjects with obesity and metabolic syndrome increases with continued change in diet and socioeconomic development.[5] The metabolic syndrome concept is easy to apply in the clinical settings, but it remains debatable if this offers clear advantages over considerations of risk factors of CKD individually *or in more specific combinations* in all populations. Future studies are necessary to determine if intensive therapy in these high-risk subjects will alter the risks of CKD or end-stage renal disease in our population or in other populations in Asia.

MATERIALS AND METHODS

Study participants

In 1985, 7824 employees (6631 men) of the Electricity Generating Authority of Thailand, aged 35–54 years were invited to participate in a survey of vascular risk factors, and 3499 (2702 men and 797 women) volunteered. In 1997, the same individuals were resurveyed using similar methods. The details had been described.[23,24] The methods are provided here in brief, as well as additional related information.

All participants completed a self-administered questionnaire and underwent a physical examination by trained medical personnel. Circumferential measurements of the waist at the umbilicus were carried out with the participant standing and rounded to the nearest centimeter. A single BP measurement was made after 5 min rest, using a calibrated mercury sphygmomanometer. Systolic BP and diastolic BP were recorded as the first and fifth Korotkoff sounds, respectively. Blood samples were drawn after 12 h overnight fast for lipids, glucose, and creatinine. The study was approved by the ethical committees of Electricity Generating Authority of Thailand and Ramathibodi Hospital. Written informed consent for each participant was obtained.

Laboratory measurements and determination of renal function

Details of laboratory methods have previously been published.[24] Lipids were measured using enzymatic calorimetric assays according to the manufacturer's instructions. Chylomicrons, very-low-density lipoprotein, and low-density lipoprotein cholesterol were precipitated by the addition of phosphotungstic acid and magnesium ions.[25] HDL-c, which remained in the supernatant was determined spectroscopically after the addition of the cholesterol reagent (Monotest cholesterol, Boehringer Mannheim, Mannheim, Germany). Serum TG was determined by colorometry method from the liberated glycerol after enzymatic hydrolysis (Peridochrom triglycerides, Boehringer Mannheim, Mannheim, Germany). Low-density lipoprotein cholesterol was calculated from the Friedewald and Fredrickson formula.[26]

sCr was measured using a modified kinetic Jaffe reaction by the same laboratory in both surveys.[23,24] Coefficients of variation for sCr were 4.96% at 1.29 mg/dl, and 5.3% at 4.0 mg/dl. Stable quality control was maintained throughout. The medians of sCr for participants with the same age range without hypertension or diabetes in 1985, and the 1997 surveys showed no significant drift.

The medians of sCrs were 1.21 mg/dl for men and 0.97 mg/dl for women in the 1985 survey, and were 1.20 mg/dl for men and 0.91 mg/dl in 1997.

The sCr values were adjusted by a two-step process, as published previously.[23,27] First, NHANES III sCr values were calibrated to the modification of diet in renal disease laboratory, requiring a correction factor of 0.23 mg/dl.[28] The mean sCr values for each gender and age group from our study were then aligned with corrected mean sCr of the corresponding group from the NHANES III study.[29] The adjusted sCr was then used to determine the eGFR according to the abbreviated modification of diet in renal disease formula as follows:[28]

$$\text{eGFR (ml/min per 1.73m}^2) = 186.3 \times \text{sCr}^{-1.154} \times \text{Age}^{-0.203} \quad (\times 0.742 \text{ for women})$$

Definitions

CKD is defined as eGFR <60ml/min/1.73m^2[28] *Diabetes* is defined as a fasting glucose above 126 mg/dl or a reported history of diabetes mellitus. *Metabolic syndrome* is defined using the following criteria.

NCEP ATP III (METS-NCEP$_{\text{ATP III}}$) includes individuals with three or more of the following five components:[30] (1) abdominal obesity-ATP III (waist circumference >102 cm for men, or >88 cm for women); (2) *high TG*($\geqslant 150$ mg/dl); (3) *low HDL-c* (men <40 mg/dl or women <50 mg/dl); and (4) High BP (systolic BP $\geqslant 130$ or diastolic BP $\geqslant 85$ mm Hg or treatment of hypertension); and (5) High fasting glucose NCEP (FG $\geqslant 110$ mg/dl). *NCEP modified* (METS-NCEP$_{\text{Mod}}$) uses a modified abdominal girth cutoff to define abdominal obesity-Asia (waist circumferences >90 cm for men, or >80 cm for women).[13] *IDF* (METS-IDF) requires the presence of abdominal obesity according to ethnic-specific cutoff waist circumference[3] (waist circumferences >90 cm for men, or >80 cm for women, which is identical to the criteria used in NCEP$_{\text{Mod}}$) plus any two or more of the following: (1) high TG (TG $\geqslant 150$ mg/dl or treatment for this abnormality), (2) low HDL-c (HDL-c <40 mg/dl in male subjects and <50 mg/dl in female subjects or treatment for this abnormality), (3) high BP (systolic BP $\geqslant 130$ or diastolic BP $\geqslant 85$ mm Hg or treatment of hypertension), (4) high fasting glucose-IDF (FG $\geqslant 100$ mg/dl or previously diagnosed type II diabetes).

Outcome measures

Only participants with complete baseline data for sCr and all metabolic syndrome components are included for analysis. Two outcome measures are investigated. The first is the prevalence of CKD among the subjects at baseline. The second is the incidence of new CKD after 12 years follow-up. The latter is determined from the *New CKD subgroup* defined as subjects with no CKD at entry, but developed CKD at follow-up. Participants who do not have sCr results in 1997, are lost to follow up, or died are excluded from this subgroup.

Statistical analyses

The frequency of METS-NCEP and METS-IDF and its individual components as well as the number of metabolic syndrome components present (i.e. 0, 1, 2, 3, 4, 5) were determined. Mean values of continuous variables and percentages of categorical variables for exposures, covariates, and outcomes were calculated by metabolic syndrome status. The prevalence of CKD and incidence of new CKD were determined for subjects according to the metabolic syndrome status.

ORs of CKD, unadjusted and adjusted for age, sex, and smoking status, were calculated using logistic regression models for individual components of the metabolic syndrome, and for the presence of metabolic syndrome. We compared subjects with 1, 2, 3, 4, or 5 components with subjects having zero components. The 4 and 5 components were combined to avoid low numbers. ORs of CKD due to individual and all possible combinations of three NCEP metabolic syndrome factors were also compared with subjects having zero components to identify combinations with highest risk. Zero component was defined according to NCEP ATP III definition except for when obesity-Asia is used, when zero component was defined according to NCEP Mod.

All statistical analyses were performed using SPSS software (SPSS Version 10; SPSS Inc, Chicago, IL). Continuous data are reported as mean $\pm$ s.d. $P<0.05$ is considered statistically significant.

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